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Value of 18-Fluorodeoxyglucose Positron Emission Tomography in the Management of Patients With Cystic Tumors of the Pancreas

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Objective
To assess the reliability of 18-fluorodeoxyglucose positron emission tomography (18-FDG PET) in distinguishing benign from malignant cystic lesions of the pancreas.

Summary Background Data
The preoperative differential diagnosis of cystic lesions of the pancreas remains difficult: the most important point is to identify malignant or premalignant cysts that require resection. 18-FDG PET is a new imaging procedure based on the increased glucose metabolism by tumor cells and has been proposed for the diagnosis and staging of pancreatic cancer.

Methods
During a 4-year period, 56 patients with a suspected cystic tumor of the pancreas underwent 18-FDG PET in addition to computed tomography scanning, serum CA 19-9 assay, and in some instances magnetic resonance imaging or endoscopic retrograde cholangiopancreatography. The 18-FDG PET was analyzed visually and semiquantitatively using the standard uptake value. The accuracy of 18-FDG PET and computed tomography was determined for preoperative diagnosis of a malignant cyst.

Results
Seventeen patients had malignant tumors. Sixteen patients (94%) showed 18-FDG uptake with a standard uptake value of 2.6 to 12.0. Twelve patients (70%) were correctly identified as having malignancy by computed tomography, CA 19-9 assay, or both. Thirty-nine patients had benign tumors: only one mucinous cystadenoma showed increased 18-FDG uptake (standard uptake value 2.6). Five patients with benign cysts showed computed tomography findings of malignancy. Sensitivity, specificity, and positive and negative predictive values for 18-FDG PET and computed tomography scanning in detecting malignant tumors were 94%, 97%, 94%, and 97% and 65%, 87%, 69%, and 85%, respectively.

Conclusions
18-FDG PET is more accurate than computed tomography in identifying malignant pancreatic cystic lesions and should be used, in combination with computed tomography and tumor markers assay, in the preoperative evaluation of patients with pancreatic cystic lesions. A positive result on 18-FDG PET strongly suggests malignancy and, therefore, a need for resection; a negative result shows a benign tumor that may be treated with limited resection or, in selected high-risk patients, with biopsy, follow-up, or both.

Cystic neoplasms of the pancreas are increasingly observed in clinical practice because of the wider use of ultrasonography and computed tomography (CT).[1] In fact, more incidental lesions are now being diagnosed.[2] Although typical radiologic features have been described, misdiagnosis and mistreatment of these tumors are not infrequent.[3–5]

Several procedures have been reported as potentially useful for differential diagnosis, such as cyst fluid cytology, cyst fluid tumor markers determination, and K-ras oncogene mutation.[6–10] However both false-negative results and seeding of malignant cells along the percutaneous tract may occur.[7,9,11–13] Endoscopic ultrasonography has been proposed as a reliable modality for differentiating pancreatic

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cystic disease, but it failed to distinguish adenocarcinoma from adenoma.[14]

The crucial problem is, obviously, to distinguish malignant from benign lesions; another important point is to evaluate when surgery is indicated for asymptomatic patients with a cystic mass of the pancreas.

18-fluorodeoxyglucose positron emission tomography (18-FDG PET) is a novel, noninvasive imaging procedure based on the principle of specific tissue metabolism, because of selective 18-FDG uptake and retention by malignant cells. Positron emission tomography has been proposed as a valuable technique for diagnosing and staging different malignancies,[15–17] including pancreatic adenocarcinoma.[18–21]

The aim of this study was to evaluate the usefulness of 18-FDG PET in the clinical management of patients with cystic lesions of the pancreas and in identifying those cystic tumors, in asymptomatic patients, that require resection because of actual or potential malignancy. To our knowledge, no other report on this topic has been published so far.

METHODS

From February 1996 through January 2000, 56 patients with suspected cystic tumor of the pancreas (n = 45) or intraductal hypersecreting mucinous neoplasm (n = 11) were prospectively investigated with 18-FDG PET. All patients underwent helical CT scanning and serum CA 19-9 tumor marker determination (RIA, Centocor Inc., Malvern, PA; serum reference <37 U/mL). The preoperative workup also included abdominal ultrasound (n = 56), magnetic resonance imaging (n = 33), and endoscopic retrograde cholangiopancreatography (n = 3).

18-FDG PET images were obtained using a dedicated Siemens machine (ECAT EXACT 47, Erlangen, Germany) with a field of view of 16.2 cm. The resolution of transaxial images was 6.0 mm full width at half maximum (FWHM) with an axial resolution of 5 mm FWHM.

After an overnight fast, PET was performed by injection of 444 MBq (12 mCi) 18-FDG intravenously. To avoid interference resulting from hyperglycemia, the patient's blood glucose level was checked just before the procedure and lowered to less than 120 mg/dL with insulin administration when necessary. Two transmission scans of the abdomen, 15 minutes each, were obtained by $^{68}Ge/^{68}Ga$ rod sources before the FDG administration to obtain cross-sections for attenuation correction of the emission images. Then two emission scans, 15 minutes each, were acquired, starting 60 minutes after FDG administration. Skin marks were made using a laser device for proper repositioning of the patient for transmission and emission scans. The reconstruction was performed in a 128 × 128 matrix with Hanning filter 0.3 cutoff. Transaxial, coronal, and sagittal sections were obtained for visual analysis, performed according to a color scale.

To perform quantitative analysis, the standardized uptake value (SUV) was calculated in the suspected neoplastic foci (SUV = tissue tracer concentration/injected dose/body weight). For the SUV analysis, a circular region of interest was placed over the area of maximal focal FDG uptake suspected to be a tumoral focus, and the mean radioactivity values were obtained. Positivity was assumed when a focal uptake occurred with an SUV of at least 2.5.

The PET scan was interpreted by a single observer (F.C.) without knowledge of the CT scan results. Each CT scan was also interpreted by a single reader (G.L.). Validation of diagnosis was based on the pathologic findings of resected specimens, biopsy, or clinical course. Pathologic classification of the pancreatic tumors was made according to WHO histologic typing.[22]

Table 1. DISTRIBUTION OF PATIENTS BASED ON PATHOLOGY

Type of Lesion	n	Validation of Diagnosis	Mean SUV (Range)
Malignant Lesions	17	R = 8, B = 9	5.1 (2.6–12.0)
Cystadenocarcinoma	8	R = 4, B = 4	5.4 (3.3–12.0)
ACCD	5	R = 1, B = 4	4.9 (2.6–7.8)
Endocrine	2	R = 1, B = 1	6.4 (6.0–6.9)
Solid-cystic tumor	1	R = 1	SUV = 3.6
IHMN	1	R = 1	SUV = 3.9
Benign Lesions	39	R = 28, B = 10, FU = 1	
Mucinous cystadenoma	6	R = 6	
Serous cystadenoma	11	R = 8, B = 3	
Pseudocysts	8	R = 3, B = 5	
Single cyst	2	R = 2	
IHMN	8	R = 5, B = 2, FU = 1	
Other*	4	R = 4	
Total	56	R = 36, B = 19, FU = 1	

R, resection; B, biopsy; FU, follow-up; ACCD, adenocarcinoma with cystic degeneration or retention cyst; IHMN, intraductal hypersecreting mucinous neoplasm.

* Duodenal enterogenous cyst, mesenteric cyst, cystic lymphangioma, endocrine adenoma.

RESULTS

The distribution of patients, according to pathology, is summarized in Table 1. The final pathologic diagnosis was obtained after surgery in 46 patients, after percutaneous or endoscopic biopsy or brushing cytology in 9 patients, and according to follow-up in 1 patient.

There were 21 men and 35 women, with a mean age of 60.1 years (range 31–86). Forty patients (71%) were symptomatic; the most common symptoms were pain (n = 33), dyspepsia (n = 3), jaundice (n = 3), and digestive bleeding (n = 1). Ten patients had recurrent attacks of mild acute pancreatitis with elevated serum levels of amylase and lipase. Sixteen patients (29%) were asymptomatic and the pancreatic lesion was incidentally detected during investigations for unrelated disease. Mean tumor diameter was 4.06 cm (range 1.0–15.0). Nine patients had multiple pancreatic cystic lesions.

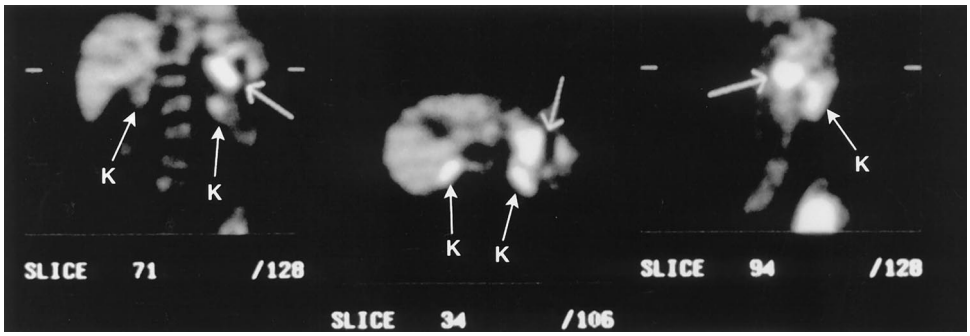

Figure 1. Positron emission tomography scan shows a focus of increased uptake (standard uptake value 5.0) within the pancreatic cyst (mucinous cystadenocarcinoma of the tail of the pancreas). The normal uptake of the kidneys is marked K. Coronal, transverse, and sagittal reconstructions (left to right).

Seventeen patients had malignant lesions (8 cystadenocarcinomas, 5 adenocarcinomas with cystic degeneration or retention cyst, 2 endocrine carcinomas, 1 solid-papillary carcinoma, and 1 intraductal hypersecreting mucinous neoplasm [papillary mucinous carcinoma, invasive type according to WHO classification]), and 39 had benign lesions.

Malignant Tumors

Of the patients with malignant tumors, there were 13 women and 4 men, with a mean age of 65.3 years (range 31–78). Fourteen patients (82%) had symptoms: 10 had abdominal pain, 3 jaundice, and 1 dyspepsia with a palpable mass. One patient with a dilated main pancreatic duct was referred to our department with the diagnosis of chronic pancreatitis; another patient was referred for septic complications after a cystojejunostomy performed elsewhere.

Three patients were asymptomatic and their lesion was incidentally found during investigations for other disease. Five of the 17 patients had diabetes.

The CT scan showed a solitary cystic mass (n = 11) with internal septa (n = 3) or multiple cysts (n = 4) or a dilated main pancreatic duct (n = 2). In one patient the CT scan showed liver metastases and in two patients encasement of the superior mesenteric vein. Mean tumor size was 5.7 cm (range 2.0–15.0). Clear CT features of malignancy were found in 11 patients (65%). Serum CA 19-9 levels were elevated in 11 of the 17 patients (65%). Ten patients had both CA 19-9 levels and CT features suggesting malignant tumor. Twelve of the 17 patients had evidence of or findings consistent with malignancy on preoperative imaging or the serum CA 19-9 assay. Sixteen of the 17 patients (94%) showed 18-FDG uptake with an SUV range from 2.6 to 12. An isolated focal uptake was found in nine patients (Fig. 1), and a peripheral uptake with central absence of metabolism was found in seven patients (Fig. 2). In three patients 18-FDG PET also showed liver metastases; these were detected by CT scanning in only one patient. In another patient PET detected 18-FDG uptake in the iliac bone that was confirmed as a bone metastasis by scintigraphy and magnetic resonance imaging. Eight patients underwent re-

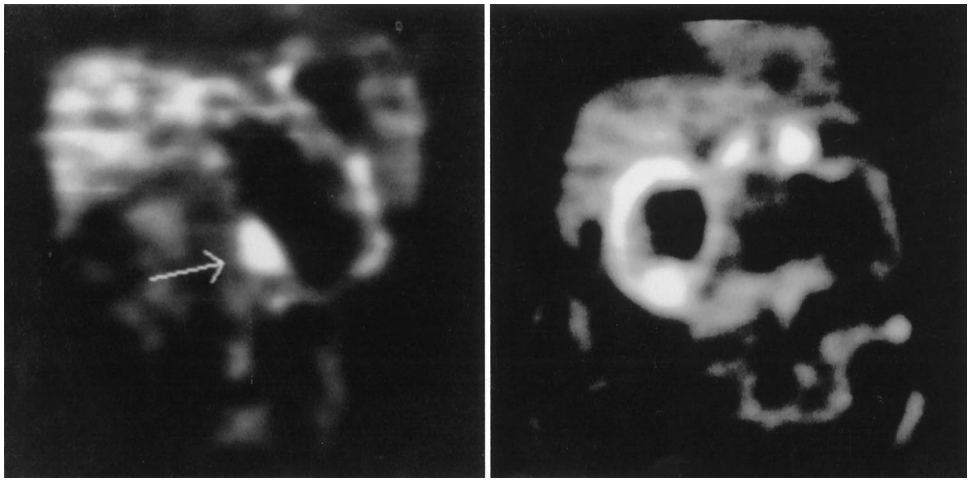

Figure 2. Positron emission tomography shows focal uptake within the cyst (standard uptake value 3.6; left) and peripheral uptake of the cystic wall (standard uptake value 6.0; right) Papillary/cystic tumor of the body and tail and neuroendocrine tumor of the head of the pancreas, respectively.

section (distal pancreatectomy and splenectomy, n = 4; pancreatoduodenectomy, n = 2; total pancreatectomy, n = 1; excision of neuroendocrine pancreatic head tumor, n = 1), three underwent bypass operation (vascular involvement, multiple liver metastases, and peritoneal involvement, one patient each). In five patients who did not undergo surgery because of poor general condition (n = 3) or multiple liver metastases (n = 2), the diagnosis was confirmed by percutaneous fine-needle biopsy.

The single patient who showed normal 18-FDG uptake was a woman with insulin-dependent diabetes with well-differentiated cystadenocarcinoma of the head of the pancreas that was treated with pancreatoduodenectomy. This tumor recurred 2 years later in the liver, and again 18-FDG PET was negative. The patient is alive 31 months after pancreatic resection.

Benign Tumors

Of the patients with benign tumors, there were 22 women and 17 men with a mean age of 57.6 years (range 31–86). Eight patients (20%) had a pseudocyst with CT features resembling a cystic tumor; a clear history of acute or chronic pancreatitis was absent in all of these patients. Twenty-six patients (67%) were symptomatic: the most common symptoms were abdominal pain (n = 23), dyspepsia (n = 2), and upper digestive hemorrhage (n = 1). In 13 patients there was a history of one or more episodes of acute pancreatitis, and 5 had diabetes. Thirteen patients (33%) were asymptomatic and their lesion was incidentally found during investigations for unrelated disease. Four patients (10%) had CA 19-9 serum levels higher than normal. Computed tomography showed a solitary cystic mass in 34 patients (with internal septations in 15) and multiple cysts with a dilated main pancreatic duct in 5 patients; the mean tumor size was 4.0 cm (range 1.0–14.0). Five patients had CT features suggesting a malignant tumor (Fig. 3), such as a mural nodule or dilation of the main pancreatic duct, which have been reported as indicators of malignancy in mucin hypersecreting tumors of the pancreas.[23] In 38 of the 39 patients no uptake of 18-FDG was shown; only 1 patient showed high uptake of 18-FDG in two abdominal areas (SUV values 2.6 and 6.8) corresponding to a 1-cm mucinous cystadenoma of the pancreatic body and a left adrenal adenoma, respectively. Four patients underwent pylorus-preserving pancreatoduodenectomy, 1 total pancreatectomy with spleen preservation, 10 distal pancreatectomy (8 with spleen preservation), 5 duodenum-preserving pancreatic head resection, 4 median pancreatectomy, 4 tumor enucleation, and 5 pancreaticocystojejunostomy. Six patients did not undergo surgery: five underwent percutaneous aspiration or endoscopic biopsy without evidence of malignancy. All patients were followed up (median follow-up 19 months; range 6–64).

Sensitivity, specificity, positive and negative predictive values, and efficiency of 18-FDG PET in detecting malignant cysts were 94%, 97%, 94%, 97%, and 96%, respectively. These figures for CT were 65%, 87%, 69%, 85%, and 80%, respectively.

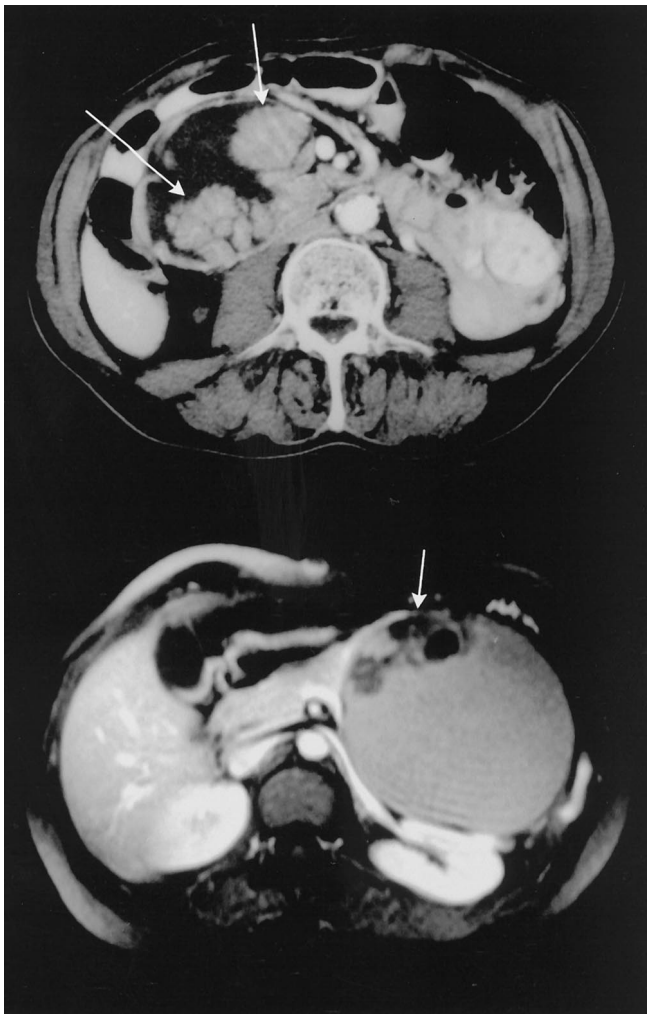

Figure 3. (Upper) Computed tomography scan of the abdomen shows marked dilation of the main pancreatic duct with solid papillary projections in this benign intraductal mucin hypersecreting tumor. (Lower) Magnetic resonance imaging of the abdomen shows a large cystic mass with mural nodules in the tail of the pancreas (mucinous cystadenoma).

Abdominal ultrasound was not evaluated in terms of sensitivity and specificity because in most of the patients it was performed elsewhere as a first-line imaging procedure before referral. Magnetic resonance imaging confirmed CT findings in 29 of 33 patients and gave additional information in 4 (12%), with clear details of the main pancreatic duct and lesions; all of them had a benign intraductal hypersecreting mucinous neoplasm.

DISCUSSION

Pancreatic cystic lesions are increasingly seen as incidental radiologic findings in asymptomatic patients or in patients with slight symptoms (i.e., dyspepsia). Preoperative

identification of malignant cysts of the pancreas is obviously important for planning appropriate treatment. However, the preoperative differential diagnosis of cystic pancreatic masses remains difficult because there are no reliable clinical or radiologic criteria to assist in making the differentiation. Serum CA 19-9 determination has been reported as a useful tool for detecting malignant cysts, with sensitivity and specificity rates of 75% and 96%, respectively.[8] Percutaneous aspiration cytology has been emphasized in the diagnosis of pancreatic masses, but cytologic diagnosis based on the fine-needle aspiration of cystic content lacks sensitivity.[11,12] Analysis of aspirated cyst fluid for enzymes and tumor markers has been suggested as a method for providing a differential diagnosis of pancreatic cystic lesions. However, a wide overlap of tumor marker values has been found between benign and malignant tumors.[24] Further, there may be a risk of seeding malignant cells.[7,13]

In recent years 18-FDG PET imaging has been increasingly used to identify and stage many types of tumors. During the process of malignant transformation, the majority of cells become avid glucose scavengers, with increased glucose transport and utilization. This enhanced glucose uptake explains why 18-FDG PET can functionally identify malignant tissues. Previously published series involving 18-FDG PET in the evaluation of pancreatic adenocarcinoma reported a sensitivity ranging from 82% to 100% and a specificity of 67% to 100%.[25–27] Rose et al[19] reported a sensitivity of 92% and a specificity of 85% in detecting pancreatic cancer for 18-FDG PET versus 65% and 62% for CT scanning. However, the role of 18-FDG PET in the evaluation of pancreatic cystic tumors has not been previously investigated.

We found that 18-FDG PET was able to detect 16 of 17 malignant cysts (sensitivity 94%) with a specificity of 95%. Further, 18-FDG PET added new information about tumor extension in three patients, showing liver and iliac bone metastases not seen by traditional imaging. The usefulness of PET scanning in staging pancreatic carcinoma has been suggested,[28–30] but conflicting data have also been reported.[31,32] The single false-negative result in our series occurred in a patient with insulin-dependent diabetes: false-negative results have been reported in patients with diabetes,[33–35] probably because of increased competition for glucose uptake. However, Friess et al[36] noted no variation in the accuracy of FDG PET on the basis of serum glucose levels. Based on the clinical presentation, CT features, and serum CA 19-9 levels, malignancy was correctly suggested in 12 patients (70.5%). In the remaining five patients 18-FDG PET showed areas of high metabolism, suggesting malignant tissue. The only false-positive result occurred in a patient with a mucinous cystadenoma, which is considered a premalignant lesion that requires resection. A similar false-positive 18-FDG PET result was reported by Keogan et al[18] in a patient with a mucinous cystic tumor; on the basis of this limited experience, they suggested that 18-FDG PET scanning should not be used to distinguish benign from malignant cystic tumors. A false-positive PET result has also been reported in a patient with serous cystadenoma.[37] In our experience, 38 of 39 benign lesions (97.4%) showed no activity of 18-FDG. A negative PET scan in our series led to a more limited pancreatic resection whenever possible (n = 18) or avoided unnecessary splenectomy (n = 9) or laparotomy in asymptomatic patients (n = 6). Further, in five patients with a negative PET study, percutaneous aspiration biopsy was performed without the theoretical risk of seeding malignant cells.

A limitation of 18-FDG PET is that this functional imaging modality cannot replace anatomic imaging in the assessment of local tumor resectability. Thus, 18-FDG PET is a sensitive and specific adjunct to CT when applied in the preoperative differential diagnosis and staging of pancreatic cystic tumors. The relatively high cost of PET scanning is clearly balanced by the number of malignancies detected in addition to CT and the CA 19-9 assay, and by avoiding unnecessary, invasive, and expensive procedures (i.e., endosonography, percutaneous or endoscopic aspiration biopsy, cyst fluid analysis) in most patients with negative PET scans. Magnetic resonance imaging in our experience should be used only to define intraductal changes in patients with intraductal hypersecreting mucinous neoplasm.

18-FDG PET provides an alternative approach to the diagnosis and treatment of pancreatic cystic tumors. When the lesion shows high 18-FDG uptake, the high likelihood of malignancy justifies the resection even in asymptomatic patients. If no uptake of 18-FDG occurs, the lesion is likely to be benign and a resection with a limited loss of pancreatic parenchyma may be considered. In asymptomatic, older patients with PET-negative pancreatic lesions, percutaneous biopsy, follow-up, or both may be a reasonable alternative to surgery.

In conclusion, based on our data, we suggest the use of 18-FDG PET in combination with serum CA 19-9 determination and CT as the only preoperative workup of patients with cystic lesions of the pancreas.

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